Update
Le point

Articles in the ***Update*** *series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.*

Les articles de la rubrique ***Le point*** *fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.*

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Nutritional anaemia—a major controllable public health problem

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Nutritional anaemia, due chiefly to iron deficiency, is widely prevalent in many parts of the world. There is increasing evidence that even mild anaemia affects health and reduces productivity and that a high prevalence of anaemia has profound socioeconomic consequences. The pathogenesis of nutritional anaemia is now reasonably well understood. Measures avilable for combating it include: therapeutic supplementation for accessible population groups with a high prevalence of anaemia, such as pregnant women and schoolchildren; iron fortification of one or more widely consumed foodstuffs; management of those conditions, such as hookworm infestation, that increase requirements for haemopoietic nutrients; and education of the public, and of all categories of health personnel, regarding the importance of anaemia and the ways of controlling it. Experience has shown that there is no simple solution to the problem and in each area where iron deficiency anaemia is prevalent it will probably be necessary to develop and combine many or all of these measures. In each community it will be necessary to introduce these measures so that their effectiveness can first be studied in a pilot trial. When this has been successfully completed it should be followed by a field trial under realistic conditions, and only when this has proved successful should a regional or national programme be introduced. However, the problem is complex and it is only by sustained effort of all concerned that it will prove possible to develop adequate public health control of nutritional anaemia.

It is well known that there are many possible causes of anaemia. However, surveys in many countries indicate that, from the public health point of view, there are three broad categories:

(*a*) nutritional anaemia;

(*b*) anaemia associated with chronic infections or infestations; and

(*c*) anaemia associated with hereditary abnormalities of the haemoglobin molecule (including thalassaemia).

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These categories are not mutually exclusive, and there is frequently overlap among them. Some infestations, e.g., hookworm, increase the requirement for haemopoietic nutrients and accelerate the development of nutritional deficiency. Moreover, in a community with a high prevalence of nutritional anaemia, there may also be a high prevalence of anaemia due to haemoglobinopathy.

This article is concerned with nutritional anaemia, which is not only the most widespread type of anaemia but also that which is most easily improved by public health measures. Unless otherwise qualified, the term anaemia in the following pages means nutritional anaemia.

Definition of nutritional anaemia

Nutritional anaemia may be defined as a reduction in haemoglobin concentration below that which is normal for the individual, due to an inadequate supply of haemopoietic nutrients. However, problems arise when an attempt is made to define a " normal " con-

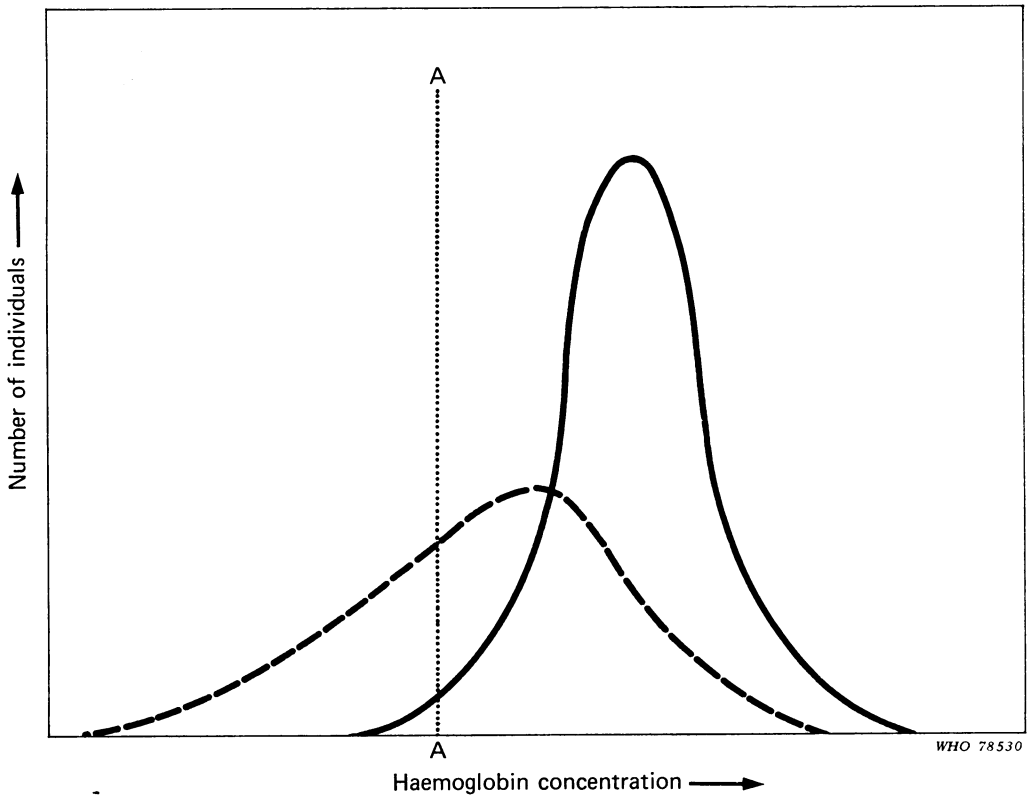

Fig. 1. Diagrammatic representation of frequency distribution curves of haemoglobin concentration in a normal non-anaemic population (solid line) and in a population with a high prevalence of anaemia (dotted line). The vertical line A–A represents the arbitrary cut-off point " below which anaemia is likely to be present ". A small proportion of normal subjects have a haemoglobin concentration below the cut-off point and quite a number of anaemic subjects have a haemoglobin concentration above it.

centration. In a given healthy individual who ingests and absorbs adequate amounts of haemopoietic nutrients, the haemoglobin concentration will be at a level optimal for that individual and further ingestion of haemopoietic nutrients will not increase the haemoglobin concentration. When a large group of such healthy, well-nourished individuals is studied, their haemoglobin concentrations will be found to be distributed over a range of values. If the number of persons with a given haemoglobin concentration is plotted against the haemoglobin concentration, the resulting frequency distribution curve will be Gaussian in shape, whereas in a population where anaemia is prevalent the shape of the curve is skewed to the left. In practice it has been found useful to select an arbitrary cut-off point of haemoglobin concentration below which anaemia is considered to be present (Fig. 1). It is important to notice that a small proportion of normal non-anaemic subjects i.e., those who do not respond to the administration of extra haemopoietic nutrients) will have a haemoglobin concentration below this arbitrary cut-off point, and that some anaemic subjects (i.e., those who do respond to extra nutrients) have a haemoglobin concentration above this cut-off point. The frequency distribution curve of normal haemoglobin concentration differs among different age groups and, after puberty, between the sexes. There is also evidence to suggest that the frequency distribution of normal haemoglobin concentration may differ slightly for different racial groups.

A World Health Organization Scientific Group has suggested arbitrary cut-off points below which anaemia is likely to be present in individuals living at sea level (Table 1). Persons with haemoglobin concentrations below these cut-off points have a high probability of being anaemic (i.e., of demonstrating a rise in haemoglobin concentration following appropriate therapy). There will be a small proportion of normal subjects with haemoglobin concentration below these cut-off points who will not show a rise in haemoglobin concentration when supplied with extra haemopoietic nutrients, but the precise percentage in the different groups has not been clearly defined. Nevertheless, these arbitrary values serve as useful guidelines and the greater the percentage of the population with haemoglobin concentrations below the cut-off point, the greater is the problem of anaemia in the community.

Table 1. Haemoglobin levels below which anaemia is likely to be present in populations living at sea level, as recommended by the World Health Organization [a]

Group	Haemoglobin (g/100 ml)
Children 6 months—6 years	11
Children 6—14 years	12
Adult males	13
Adult females (nonpregnant)	12
Adult females (pregnant)	11

[a] From WHO Technical Report Series, No. 405, 1968, p. 9.

Etiology of anaemia

Although many nutrients are involved in the production of red cells and haemoglobin, iron deficiency is by far the commonest cause of nutritional anaemia all over the world. In certain sections of the population, especially pregnant women, folate deficiency is also an important cause. In some individuals, vitamin B_{12} deficiency may produce severe anaemia, as in classical pernicious anaemia; however, this is relatively rare and even in countries such as India, where the population subsists on a largely vegetarian diet with a marginally

adequate vitamin B_{12} intake, there is little evidence from the public health point of view that vitamin B_{12} deficiency is a significant cause of anaemia. In children with severe protein–energy malnutrition, protein deficiency may play a role in the accompanying anaemia; however, less marked degrees of protein deprivation have not been shown to cause anaemia. Deficiencies of other vitamins and some trace elements may also produce anaemia, but there is as yet no evidence that these are of public health importance. This article will therefore deal mainly with anaemia due to iron deficiency and to some extent with that due to folate deficiency.

NUTRIENT BALANCE

The normal well-nourished individual is in a state of nutritional balance in which the amount of a given nutrient absorbed from the diet is equal to the amount lost from the body plus the amount used for growth or (in the case of folate) the amount broken down by metabolic processes. This balance can be affected by a variety of factors such as a reduced dietary intake of the nutrient, decreased absorption from the intestine, increased losses from the body, or higher requirements for the nutrient. The well-nourished individual has reserves or body stores of the haemopoietic nutrients. When losses/utilization exceeds the amount absorbed these stores become depleted and, when they are exhausted, nutritional anaemia develops. Anaemia is therefore a late manifestation of nutrient deficiency.

Iron

Distribution in the body

Most of the iron in the body is in haemoglobin, which contains 3.4 mg of iron per gram. There is also iron in myoglobin and in iron-containing enzymes. The remainder of the body iron is present largely as storage iron, which can be used as needed for haemoglobin production.

Losses

Iron is lost from the body via the gastrointestinal tract, the skin, and the urine. These basic losses occur in all individuals and are relatively constant at about 14 μg per kg of body weight per day. They have been measured by using radioactive isotopes of iron to label the body iron pool and measuring the rate at which radioactivity is lost from the body.

In addition to the basic losses, women of reproductive age lose iron in the menstrual discharge. Menstrual blood losses have been measured in groups of women in several parts of the world and in each study similar results have been obtained. In a given individual the amount of blood lost each month is fairly constant, so that it is possible to construct a frequency distribution curve of the amount of menstrual iron loss. The curve is skewed, with 90% of women losing an average of up to 1.4 mg of iron per day and the remaining 10% having average losses of 1.4–3 mg or more per day.

Iron is also lost from the body as a result of any pathological condition involving blood loss. By far the commonest cause of this is hookworm infestation, which affects many millions of people living in tropical and subtropical areas. The worms live in the small intestine, suck blood from the mucosa, and discharge the red cells into the lumen of the host's gut. These red cells then undergo digestion and some of the iron is reabsorbed. Isotopic studies have shown that the net daily iron loss from a worm load represented

by an egg count of 1000 eggs/g of faeces is 0.8 mg for *Necator americanus* and 1.2 mg for *Ancylostoma duodenale*. Other parasites such as *Trichuris trichuria* and *Schistosoma* spp. also cause blood loss and heavy infestations may produce iron deficiency anaemia.

In the past, the high prevalence of iron deficiency anaemia in the tropics has sometimes been attributed to increased iron loss due to excessive sweating. However, the iron content of sweat appears to be chiefly due to the iron in shed epithelial cells, and isotopic studies have failed to show that excessive sweating produces increased iron loss.

Utilization

Iron requirements increase when the individual is growing and during pregnancy and lactation. During periods of growth, extra iron is needed for the expanding haemoglobin, myoglobin, and iron-containing enzyme pools, and the more rapid the growth the greater the relative iron requirements and the greater the risk of developing iron deficiency.

During pregnancy there are no menstrual losses, but in addition to basic losses of iron (about 200 mg for the whole of pregnancy), extra iron is needed to meet the requirements of the fetus and placenta (about 300 mg) and for the expansion of the maternal red cell mass (about 500 mg). The total requirement for the whole of pregnancy is about 1000 mg but, except for the basic losses, this is concentrated in the second half of pregnancy. If there are no body iron stores to draw on, the satisfying of these needs during the second half of pregnancy would require the absorption of over 6 mg of iron per day, which can only be achieved by therapeutic supplementation. Pregnant women who do not receive supplementary iron are therefore at great risk of developing iron deficiency anaemia.

During lactation there are usually no menstrual losses but about 0.2 mg of iron is secreted daily in the breast milk. In addition, iron loss due to haemorrhage at delivery (about 250 mg) and any borrowing from iron stores that occurred during pregnancy have to be made up; on the other hand, there is some extra iron available as the red cell mass, which increased during pregnancy, returns to normal.

Absorption

The amount of iron absorbed from the intestine is closely dependent on the iron status of the individual—the lower the body iron store the greater the absorption of both therapeutic and dietary iron. Thus absorption from a test dose of 3 mg of iron in the form of freshly prepared iron(II) ascorbate labelled with a radioactive isotope of iron, given in the fasting state, may vary from less than 10% in the iron-replete subject to over 90% in the severely iron deficient. The absorption from such a test dose may be used to characterize the iron status of the subject; hereafter it is referred to as the " reference dose absorption ".

Iron in the diet may be considered as being present in two main forms—haem iron in animal products and non-haem iron in vegetables, cereals, and other foods. In addition, in some dietaries, there may be a considerable amount of contamination with iron-containing soil. Studies with foods labelled with radioactive isotopes of iron have shown that haem iron and non-haem iron are absorbed by different mechanisms and that, while iron in cereals and vegetables is relatively poorly absorbed (1–6%), haem iron is much better absorbed (up to 22%).[a]

The absorption of iron from one foodstuff is also influenced by the presence of other foods. For example, the presence of meat, fish, or ascorbic acid will increase the absorption

[a] These figures were obtained from a mixed group of subjects, half of whom were iron deficient.

of vegetable iron, whereas the presence of phytates, tannins, coconut milk, or eggs decreases it. The complex interacting influences of various foodstuffs on iron absorption make it difficult to guess the availability of iron in a given diet or to predict the effect of a diet on the absorption of supplementary iron. Until more data are available, it is therefore desirable to study the absorption of the iron in the diet and the availability of supplementary iron before embarking on control programmes.

It has been shown that it is possible to study the absorption of dietary iron relatively simply by labelling the haem iron pool with haemoglobin in which a radioactive isotope of iron is incorporated, and the non-haem iron pool with a soluble iron salt labelled with another isotope. In this way, the iron absorption from a whole meal can be readily quantified. In many parts of the world the diet is largely vegetarian, or the amount of meat consumed so small that the haem iron makes an insignificant contribution to the total iron intake. In such circumstances the iron absorbed from the meal can be measured by labelling the non-haem iron pool alone. It has also been shown that this can be done by adding the label to one bulky article of the diet after cooking (e.g., the rice in a rice-based meal). This considerably facilitates the application of this technique in field studies. Because the amount of iron absorbed depends on the iron status of the individual, it is necessary to determine this status by measuring the reference dose absorption. If a number of individuals with different amounts of storage iron are studied, the iron absorbed from the diet can be plotted against the reference dose absorption. In this way it is possible to compare the iron absorption from different dietaries in different groups of subjects.

The availability of supplementary iron added to the diet can be studied in a similar fashion by labelling the supplementary iron with a radioactive isotope and characterizing the iron status of the individual by measuring the absorption from the reference dose labelled with another.

Requirements

The amounts of iron that must be absorbed each day to meet the requirements of the majority of normal individuals, as recommended by a WHO Scientific Group, are shown in Table 2. As a general guide, the amounts that should be ingested in different types of diet to achieve this level of absorption are also given. These figures do not take into account contamination iron (e.g., from soil) and in those persons on mainly vegetarian diets they may need to be considerably higher.

Folate

Distribution in the body

Folate is present in most body tissues, but the main bulk is in the liver. Well-nourished adults probably have folate stores sufficient to meet the body's requirements for up to 4 or 5 months in the absence of dietary intake.

Losses

Small amounts of folate are excreted in the urine. It is also excreted in the bile, but the majority of this is probably reabsorbed together with the dietary folate. Folate is excreted in considerable amounts in the faeces, but this is probably folate synthesized by intestinal microorganisms rather than true excretion from the body folate pool.

Table 2. Daily amounts of iron that must be absorbed and the iron intakes needed to achieve this, as recommended by the World Health Organization [a]

Group	Absorbed iron required (mg)	Iron required, according to diet (mg)		
		Animal foods below 10 % of calories [b]	Animal foods 10-25 % of calories	Animal foods over 25 % of calories
Infants 0–4 months	0.5	— [c]	— [c]	— [c]
Infants 5–12 months	0.7	7	5	4
Children 1–12 years	1.0	10	7	5
Boys 13–16 years	1.8	18	12	9
Girls 13–16 years	2.4	24	16	12
Menstruating women [d]	2.8	28	19	14
Men	0.9	9	6	5
Pregnant women 1st half of pregnancy	0.8	8	6	4
2nd half of pregnancy [e]	3.0	30	21	15
Lactating women	2.4	24	17	12

[a] From WHO Technical Report Series, No. 503, 1972, p. 17.
[b] In populations eating virtually no foodstuffs of animal origin, the intakes need to be higher.
[c] Breast-feeding is assumed to be adequate.
[d] For non-menstruating women, the recommended intakes are the same as for men.
[e] Assuming that there is a " loan " of 500 mg from body stores.

Utilization

Folate is used by the body in the synthesis of purine and pyrimidine nucleotides, which in turn are used in the synthesis of nucleic acids. Folate requirements therefore increase during periods of growth, in pregnancy, and in situations where there is rapid tissue regeneration (e.g., in persons with haemolytic anaemias).

Absorption

Folate is absorbed mainly in the upper part of the small intestine by means of a specific transport mechanism. Most of the folate in food is in the form of polyglutamates and during absorption these are probably broken down in the intestinal cells to monoglutamates. The relative availability of pteroylmonoglutamic acid and the polyglutamate forms of folate is not completely clear, although the weight of evidence suggests that the polyglutamate forms are not as available as pteroylmonoglutamic acid.

Folate is present in many foodstuffs, liver and green leafy vegetables being relatively rich sources. It is heat-labile and is readily destroyed during cooking; therefore, estimates of folate intake from food tables are of little value and the relevant data must be obtained from measurements of folate as actually eaten in the home.

Requirements

Exact estimates of folate requirements are much more difficult to obtain than those for iron. Data derived from the study of the haematological responses of individuals with folate deficiency anaemia, together with studies of indices of folate nutrition in non-anaemic

subjects on controlled folate intakes, suggest that an intake of 200 μg of pteroylmonoglutamic acid is adequate for the nonpregnant adult. However, to make allowance for the relatively poorer availability of polyglutamates, it is considered that 400 μg per day of a mixture of pteroylmonoglutamic acid and polyglutamates is needed by the average adult.

During pregnancy, folate requirements are approximately doubled owing largely to the needs of the fetus. Since most diets do not provide this amount of folate, some degree of folate deficiency is highly prevalent, even in developed countries, in the third trimester of pregnancy among women not given supplementary folate. During lactation, folate is excreted in breast milk and, in addition, any folate deficiency that occurred during pregnancy has to be made up, thus increasing folate requirements over basal levels.

Information on the folate requirements of infants and children is scanty, but they probably increase during periods of rapid growth. In the fetus, folate stores are laid down mainly in the latter part of pregnancy, so that babies born prematurely have smaller stores and are particularly liable to develop overt folate deficiency.

The daily intakes of folate recommended by a WHO Scientific Group are shown in Table 3.

Table 3. Daily intakes of folate, as recommended by the World Health Organization [a]

Group	Total folate (μg) [b]
Age group	
0–6 months	40–50
7–12 months	120
1–12 years	200
13 years and over	400
Pregnant women	800
Lactating women	600

[a] From WHO Technical Report Series, No. 503, 1972, p. 18.
[b] "Total folate" includes monoglutamate and polyglutamate forms.

THE PUBLIC HEALTH IMPORTANCE OF NUTRITIONAL ANAEMIA

Prevalence

Nutritional anaemia and haemopoietic nutrient deficiency are prevalent in many parts of the world. Even in developed countries certain sections of the population, such as premature infants, preschool children, and pregnant women, are particularly at risk; in developing countries the problem is much more widespread and serious. For example, studies in women in the third trimester of pregnancy and not receiving supplements have shown prevalences of anaemia (haemoglobin less than 11 g/100 ml) of 26% in Latin America, 37% in Venezuela, 57–80% in India, 82% in Burma, and 84% in Thailand. However, the high prevalence of anaemia is not limited to pregnant women; in parts of Asia even adult males, who are usually least at risk, show a prevalence of anaemia (haemoglobin less than 12 g/100 ml) of up to 40% or more.

DELETERIOUS EFFECTS OF ANAEMIA

Clinicians have long suspected that anaemia has deleterious effects, but until recently there has been little scientific documentation of these.

Work output

Mild anaemia, and possibly even iron deficiency in the absence of anaemia, reduces the maximum level of work. Most daily tasks do not involve sustained physical effort; nevertheless, studies among plantation workers in Indonesia and tea pickers in Sri Lanka demonstrated that, in ordinary occupations, anaemic individuals had a decreased work output compared with that of non-anaemic colleagues. Moreover, appropriate treatment significantly increased the productivity of the anaemic workers. The mechanisms responsible for this effect are not fully understood. Severe anaemia limits the oxygen-carrying capacity of the blood and may limit maximum work output, but in the performance of ordinary tasks and with milder degrees of anaemia, this is unlikely to be the explanation and other factors are probably important. Recent studies on rats have shown that iron deficiency, even in the absence of anaemia, reduces work capacity owing to striated muscle dysfunction associated with reduction in the activity of the muscle enzyme glycerol-3-phosphate dehydrogenase (EC 1.1.99.5). This abnormality is rapidly reversed following iron therapy. It is not yet known whether this abnormality occurs in iron-deficient humans but, whatever the mechanisms responsible, it is evident that even moderate degrees of anaemia, and perhaps even deficiencies of haemopoietic nutrients in the absence of anaemia, may have profound socioeconomic consequences.

Pregnancy

In pregnancy, severe anaemia is associated with an increased risk of premature delivery and increased fetal and maternal morbidity. Milder degrees of anaemia may also be detrimental and have been shown to be associated with premature delivery, lower birth weight, placental hypertrophy, and increased maternal estriol excretion.

Other effects

In severe iron deficiency, it has been demonstrated *in vitro* that the phagocytic activity of leucocytes is decreased and that the level of the enzyme myeloperoxidase, contained in the granulocytes, is reduced. In addition, there is impairment of lymphocyte transformation. These *in vitro* findings are difficult to interpret in terms of the susceptibility of the host to infection; some studies have suggested that iron-deficient anaemic people may be more prone to respiratory infections, but further evidence is needed before any firm conclusion can be reached.

Iron deficiency has been shown to produce histological changes in various tissues, such as the oral and pharyngeal mucosae and the nails. Widespread ultrastructural abnormalities also occur in the mitochondria of a number of different body cells, but the functional significance of these changes is not known.

CONTROL OF NUTRITIONAL ANAEMIA

Determining the extent of the problem

In many countries, there is already sufficient information on the prevalence of nutritional anaemia. Where this information is not available, appropriately planned surveys should be carrried out. Ideally, surveys should include a statistically valid sample of the population but, where this is not possible, a study of women in the third trimester of

pregnancy who are not receiving supplements will give some indication of the severity of the problem in the community. The simplest measurement for such surveys is that of haemoglobin concentration and/or haematocrit—either or both of these should be carried out under carefully standardized conditions with appropriate controls. If, in addition, it is possible to make other measurements, such as serum iron concentration, percentage saturation of transferrin, free erythrocyte protoporphyrin, serum ferritin, and serum and red cell folate concentrations, then it will be possible to arrive at some conclusion as to the probable cause of the anaemia. Such information should, however, be confirmed by appropriately designed therapeutic trials. It should be noted that if it is not possible to carry out the other measurements, it is still possible to obtain adequate information by measuring the haemoglobin concentration (and/or haematocrit) followed by appropriately designed therapeutic trials. Where there is a known or suspected high prevalence of haemoglobinopathy or diseases that may produce anaemia, such as malaria, appropriate tests must be carried out to identify the affected individuals. These persons must be considered in a separate category both for determining prevalence and in the planning of therapeutic trials.

When the prevalence of nutritional anaemia is known, a decision must be made regarding its significance in relation to other health needs of the community and appropriate action planned according to available resources.

Measures available for the control of nutritional anaemia may be considered broadly under three headings:

1. Therapeutic supplementation.
2. Fortification of the diet.
3. Ancillary measures, such as parasite control and educational campaigns.

These measures are not mutually exclusive and may be applied together in an integrated approach to the problem.

In the past, it has often been assumed that nutritional anaemia can be dealt with merely by " giving iron pills " or increasing iron intake by fortifying food, e.g., wheat flour used in bread manufacture, with iron. A number of such schemes, instituted in different parts of the world, have been shown to be inadequate or totally ineffective because they were introduced on the assumption that they would cure anaemia without demonstration of their efficacy. It is now clear that owing to many factors, such as conditions affecting the availability of iron in the diet and the influence of economic and social customs, it is essential that any intervention programme be introduced in a methodical fashion that enables its efficacy to be tested step by step. First, a pilot scheme should be introduced; when this has been shown to achieve the desired results it should be followed by a trial under realistic field conditions. Only when a field trial has proved successful should a regional or national programme be introduced.

Therapeutic supplementation

Iron

When there is a high prevalence of iron deficiency anaemia, and especially when there is a need to improve the situation in a short space of time (e.g., in pregnancy), relatively large amounts of additional iron must be supplied. The only way this can be achieved is by therapeutic supplementation either in the form of iron tablets or, in the case of young children, a liquid preparation. Theoretically, it can also be achieved by parenteral iron

injections, but the expense and risks both of allergic reactions and possible late oncogenic effects make this approach both impractical and unjustified for public health use.[a] There is a bewildering variety of oral iron preparations available that differ widely in their content and availability of iron and in cost. Since it has been shown that the prevalence of side effects from oral iron therapy is closely related to the concentration of soluble iron ions rather than to the precise inorganic salt, there seems to be no reason not to use the cheapest iron salt, iron(II) sulfate.

The physical conditions under which tablets are made, the nature of the excipient, and the type of coating may all influence the availability of the iron *in vivo*. For example, some tablets pass intact through the gastrointestinal tract. It is therefore essential that the tablets employed supply readily available iron, and since there may be wide intra-batch variations, it is necessary to test the availability of iron in each batch of tablets. This is best done by studying the rise in plasma iron concentration 2–3 hours after the administration to fasting subjects of a test dose of tablets containing 100–150 mg of iron and comparing it with the rise obtained after an equivalent amount of iron has been given as a freshly prepared solution of iron(II) sulfate. Such tests should be carried out in a group of 6–10 persons, some of whom should be given the tablets first and the others given the solution first, the two tests being performed a week apart. To be acceptable, the rise in serum iron concentration following ingestion of the tablets should be at least 70% of that following ingestion of the solution.

From available information, it is possible to make approximate calculations of the amount of iron that must be absorbed each day in order to achieve the desired effect within a given period of time. Thus, the total amount is given by the sum of:

(*a*) daily basal iron losses: 14 μg/kg $\times$ number of days;

(*b*) additional iron losses caused by menstruation, hookworm infestation, etc.;

(*c*) additional demands caused by pregnancy, growth, etc.;

(*d*) amounts necessary to treat existing anaemia; and

(*e*) amounts needed to replenish body stores.

This sum, divided by the number of days over which therapy is planned, will indicate the amount of iron that must be absorbed each day to achieve the desired result.

As an example, consider the supplementation of women during the last 16 weeks of pregnancy. If it is assumed that basal iron losses are 14 μg/kg, that the average body weight is 50 kg, that the iron requirements of pregnancy are 500 mg for increase in maternal haemoglobin mass and 300 mg for fetus and placenta, that the haemoglobin concentration is 8 g/100 ml and it is desired to raise it to 12 g/100 ml by term, and that no account is made for abnormal losses due to hookworm infestation and no attempt is made to replenish body stores, then the iron requirements are:

Basal losses ($0.014 \times 50 \times 112$)	78 mg
Increase in haemoglobin mass	500 mg
Iron for the fetus and placenta	300 mg
Iron required to raise the haemoglobin level from 8 to 12 g/100 ml	400 mg
Total	1278 mg

[a] The recently introduced iron-poly(sorbitol-gluconic acid) complex, which so far appears not to induce allergic reactions and which can provide up to 500 mg of iron at a time, may be of potential use in public health programmes.

Therefore, the daily amount that must be absorbed during the 16 weeks is 1278/112=11.4 mg. This figure includes the iron available from the diet. If this is assumed to average 1 mg per day, then it will be necessary to absorb approximately 10 mg of supplementary iron per day. If the iron absorption from a supplement over the period averages 5%, then 200 mg of elemental iron par day should theoretically be adequate. However, with currently available iron formulations, this amount of iron given in one dose may produce a high incidence of undesirable side effects and it may be better to give 100 mg twice a day.

Folate

As with iron, folate supplementation will most often be required when there is a high prevalence of folate deficiency and it is necessary to improve the situation in a relatively short time. Since the amounts of folate required are not known with the same precision as those of iron, and since the availability of dietary folate cannot readily be measured, the amount of supplement required in a given situation is not so easily calculated.

The daily requirement during the latter half of pregnancy is probably in the region of 800 μg. This is more than is present in most diets so that it is not surprising that there is a high prevalence of folate defiency in pregnant women who are not receiving a supplement. However, the additional amount needed to meet the requirements is not well defined. Some studies on pregnant women in developed countries have shown that daily supplements of 100–300 μg of pteroylmonoglutamic acid, in addition to the dietary intake, are sufficient to prevent the development of overt folate deficiency. However, this will obviously depend on the amount of folate present in the basal diet and on the availability of the supplementary folate.

When trials of iron supplementation are carried out it has been the custom to give larger amounts of folate (e.g., 5 mg/day) to ensure that folate deficiency does not limit the haematological response to iron. However, there is no doubt that this amount is unnecessarily large and could safely be reduced to 1 mg/day and still provide excess folate.

Since, compared with iron, folate is readily absorbed and since tablet production and distribution cost far more than the folate in the tablet, it may not be necessary for supplementation purposes to define more precisely the minimum amount of additional folate required. However, if it is desired to do so, it will have to be done by means of a pilot trial employing optimal amounts of iron and different amounts of folate.

In any supplementation programme employing folate it is important that the stability of the folate in the tablets is assured under the extremes of conditions likely to be encountered in the field.

The administration of folate supplements to persons with severe vitamin B_{12} deficiency may theoretically precipitate neurological damage. However, women in India have for years been given iron and folate supplements during pregnancy and there is no recorded case of such a complication. Therefore, from the public health point of view, this risk would appear to be negligible.

Supplementation trials

When a decision has been made regarding dosage, a pilot supplementation trial should be carried out to determine whether the calculated amount of supplementary iron is adequate and whether folate supplementation is also necessary.

Before the pilot trial is undertaken, a preliminary survey should be made to determine whether there are other factors present that may affect the response to supplementation,

such as haemoglobinopathies, heavy hookworm infestation, a high prevalence of malaria, or ethnic differences. If so, it is desirable to separate these women and study their response to supplementation separately so that the effects of the various factors can be determined.

When a pilot supplementation trial has been successfully carried out, a field trial should be performed in a limited area as far as possible representative of the conditions that apply in the region or country, utilizing either existing public health channels for tablet distribution or such channels as could reasonably be duplicated on a regional or national scale (e.g., the distribution of supplements to schoolchildren by teachers). Supplementation on a regional or national basis should be implemented only when a field trial has been successfully carried out.

Fortification

Supplementation can reach only selected groups in the community and requires a special infrastructure for its implementation. Fortification, on the other hand, provides a way of increasing nutrient intake without the need to ensure the cooperation of the consumers. Theoretically, this approach can be used for increasing the intake of any haemopoietic nutrient but, because of the predominance of iron deficiency, the discussion will be confined to iron fortification. The amounts of additional iron that can be made available by this means are limited. This approach therefore offers a solution for the longer term and is best suited to those situations where there is a mild to moderate degree of iron deficiency; where deficiency is severe, it can also be combined with a supplementation programme.

In planning iron fortification, the first task is to find a suitable vehicle and an appropriate form of iron to be added to it. The vehicle must be: (*a*) a foodstuff that is consumed in adequate amounts by the majority of the target population; (*b*) one that is processed or available at relatively few centres in a country or region so that fortification can be effectively carried out; and (*c*) one that is not adversely affected by the addition of the fortifying agent (e.g., in terms of taste, colour, storage, or cooking properties). Possible vehicles in use, or being explored for use, in iron fortification programmes are wheat flour (Norway, Sweden, the United Kingdom, and the United States), sugar (Guatemala), salt (India, Indonesia, the Philippines, and Thailand), fish sauce (Thailand), sodium monoglutamate (Philippines), and processed baby foods. The iron compound used for fortification must be one: (*a*) from which the iron is readily absorbed; (*b*) which does not affect the colour or taste of the food; (*c*) which is stable in storage under extreme climatic conditions; (*d*) which is stable on cooking; and (*e*) which is relatively inexpensive. In some countries where bread is a staple food, iron(II) sulfate, reduced iron, or iron carbonyl have been used for the fortification of wheat flour. Unfortunately, most of these programmes have not been adequate evaluated, although there is some evidence that a number have not been very effective, either because of the low bioavailability of the added iron or because iron has been added in insufficient amounts.

In Guatemala, a trial is in progress employing iron(III) sodium ethylenediaminetetraacetate (EDTA) added to sugar. This has been shown to be stable during storage and cooking and the iron has a high bioavailability. When added to tea it causes a blackish discolouration, but this is not a problem in Guatemala where coffee is drunk rather than tea. Iron(III) sodium EDTA has been used successfully in the fortification of fish sauce in Thailand.

Salt has been successfully employed as a vehicle for iodine fortification in many parts of the world, and it appears also to be suitable for iron fortification. Trials of salt fortified

with iron(II) orthophosphate, together with sodium hydrogensulfate as an absorption promoter, are in progress in India. In Thailand, the use of salt fortified with iron(II) sulfate together with a stabilizer is being explored.

A full discussion of the various iron compounds that might be considered for use in fortification programmes has been published.[a]

The absorption of fortification iron is greatly influenced by the type of diet, being relatively good when meat, fish, or ascorbic acid-containing foods are present in the diet but poor when the diet is based on whole grain cereals, especially maize. Therefore, when a suitable vehicle and additive have been found, pilot tests with the radioactively labelled additive should be carried out to determine the amount of extra iron that will be absorbed when the fortified vehicle is added to the local diet. Such tests should be carried out in a group of persons with different body iron status characterized by absorption from the reference dose. Absorption of the supplement at 40% of the absorption of the reference dose will then give a measure of the expected increase in iron absorption by individuals on the borderline of iron deficiency. This will indicate whether fortification is likely to be effective and, if so, the benefit to be expected from supplementation in a given period of time. For example, if isotope tests show that a 10-mg supplement results in an increase of 0.5 mg of iron at a reference dose absorption of 40%, a person with iron deficiency anaemia weighing 50 kg will take about 240 days to absorb enough iron to show an increase in haemoglobin of 1 g.

Where the nature of the diet is such that iron fortification does not produce an adequate increase in iron absorption, it may prove possible to enhance iron absorption, for example by the addition of ascorbic acid, but such an approach is still very much in the experimental stage and has never been tested in a field trial.

Once pilot studies have confirmed the feasibility of fortification, a field trial should be carried out. Such a trial must clearly be carried on for a much longer time than is needed for supplementation, and a period of at least 2 years should be planned with yearly measurements of haemoglobin concentration and/or haematocrit and whatever other indices of iron nutrition are possible.

As with any trial, it is essential to have a suitable control group so that the influence of factors other than the food fortification can be assessed. Ideally, a randomly selected half of the study families in a given community or area should receive the unfortified vehicle. However, in practice this is usually impossible to arrange and two matched but separate communities will have to be studied, one of which receives the fortified vehicle and the other the vehicle from the same source but without the fortifying agent.

The number of individuals who must be included in a field trial will depend on a variety of factors such as the prevalence, severity, and cause of the iron deficiency, the expected drop-out rate from the study, and the statistical accuracy with which it is desired to show a given effect. Special care must also be taken to ensure that the iron content of the fortified vehicle is constant and that it maintains its bioavailability throughout the duration of the study.

If a field fortification programme is shown to be successful, the next step is to embark on a regional or national programme. It is essential that any such programme has built-in mechanisms for ensuring quality control of the fortified food and for evaluating the continuing efficacy of the programme.

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[a] WHO Technical Report Series, No. 580, 1975 (*Control of nutritional anaemia with special reference to iron deficiency*: report of an IAEA/USAID/WHO Joint Meeting), p. 25.

Other measures

Where parasitic diseases are responsible for causing increased blood losses, reduction of the parasite load or eradication of the parasite will reduce iron requirements, and the heavier the original parasite load the greater the gain from elimination. However, it is important to note that parasites are usually only one factor in the pathogenesis of anaemia and even their total elimination without the provision of additional iron will seldom cure the anaemia. A detailed discussion of parasite control is beyond the scope of this article, but it is a difficult task that will involve much expenditure of time, effort, and money.

Theoretically, changing dietary patterns to increase the intake of iron and of foods that promote iron absorption, such as meat, fish, and those rich in ascorbic acid, will help to improve the iron balance. However, it is notoriously difficult to change dietary patterns and at best this is a very long-term approach to the problem.

A combined approach

Experience to date indicates that in regions where there is a high prevalence of anaemia there is unlikely to be any simple public health solution to the problem. To achieve success it will probably be necessary to develop and combine a number of different approaches including:

1. Supplementation programmes for groups most at risk and groups that can readily be reached through already existing distribution channels or those that could be developed, such as schoolchildren, pregnant women, and groups of workers on estates or in large industrial complexes. Side effects caused by existing oral iron preparations limit the amount of iron that can be given in one dose and there is an urgent need to develop a cheap preparation with a high availability of greater amounts of iron but with a low incidence of side effects.

2. Fortification programmes aimed at the whole community. In each situation the best possible combination of fortifying agent and vehicle(s) needs to be worked out.

3. Fortification programmes aimed at sections of the community that may be provided with special foodstuffs, e.g., fortification of milk formulas and other baby foods.

4. Control of parasitic diseases.

5. Education of the public through all available channels, including schools, antenatal clinics, etc., to make people aware of the importance of anaemia and of the measures they can take to prevent it.

6. Education of doctors, nurses, paramedical workers, health planners, and politicians regarding the importance of nutritional anaemia and the means available for combating it.

A concerted effort to develop the necessary technology and to combine the results of technological research with well designed pilot and subsequent field trials in the most affected areas of the world should enable great strides to be made in the foreseeable future in the public health control of nutritional anaemia.

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RÉSUMÉ

L'anémie nutritionnelle : le problème et son approche en santé publique

L'anémie nutritionnelle due à une carence en nutriments hémopoïétiques se manifeste par une réduction de la concentration d'hémoglobine. Il n'existe pas de concentration « normale » d'hémoglobine uniforme mais une gamme de valeurs que met en évidence la courbe de distribution de fréquence établie pour une population saine et bien nourrie. Cette courbe est une courbe de Gauss qui se déplace vers la gauche lorsqu'elle se rapporte à un groupe de population où prévaut l'anémie (Fig. 1 — p. 660). La concentration d'hémoglobine varie selon l'âge et le sexe. Un groupe scientifique de l'OMS a suggéré l'adoption pour la pratique courante de seuils théoriques au-dessous desquels la présence d'anémie est probable (tableau 1).

Le fer est l'un des nutriments les plus importants pour la production d'hémoglobine, mais la carence en acide folique est souvent aussi à l'origine d'anémie, en particulier chez les femmes enceintes. La vitamine B_{12} et les protéines, ainsi que d'autres vitamines et divers oligoéléments jouent un rôle accessoire variable. L'équilibre nutritionnel est réalisé pour un nutriment déterminé lorsque la quantité ingérée est égale au total des pertes physiologiques (selles, urine et peau) et des besoins en relation soit avec la croissance soit avec les transformations métaboliques du nutriment. Pour le fer, présent dans l'hémoglobine à raison de 3,4 mg/g, les déperditions de base se montent quotidiennement à environ 14μg par kg de poids corporel, mais toute perte de sang (en particulier chez les femmes lors de la menstruation et chez les individus infestés par des vers ou autres parasites) entraîne une perte de fer additionnelle. Les besoins sont accrus pendant la grossesse, et notamment durant la seconde moitié de celle-ci où ils nécessitent, en l'absence de réserves, une absorption supérieure à 6 mg par jour qui ne peut être réalisée que par la supplémentation thérapeutique. La quantité de fer absorbée à partir des aliments ou d'une dose thérapeutique varie considérablement en fonction des réserves en fer de l'organisme. Les études faites avec des aliments radio-marqués ont montré que le fer hémique (contenu dans les aliments d'origine animale) était beaucoup mieux absorbé que le fer non hémique provenant de légumes ou céréales. L'absorption de fer à partir d'un aliment est aussi influencée par la nature des autres aliments consommés, qui peuvent soit l'accroître (la viande et le poisson favorisent l'assimilation du fer des végétaux), soit la diminuer (comme les œufs). Pour déterminer l'absorption de fer dans divers régimes, on peut se contenter de « marquer » au moyen de

fer radioactif un des aliments de base et de comparer l'absorption de ce fer radioactif à celle d'une dose de référence pour tenir compte des différences individuelles. Le tableau 2 (p. 665) indique la quantité de fer qui doit être absorbée par divers groupes de population normaux et la quantité de fer alimentaire qui doit être ingérée, calculée en fonction de la place plus ou moins importante que tiennent les produits d'origine animale dans l'alimentation.

L'acide folique sert à la synthèse des nucléotides puriques et pyrimidiques, eux-mêmes nécessaires à la synthèse des acides nucléiques. Les besoins sont donc accrus au cours de la croissance ou de la régénération rapide des tissus. Les polyglutamates des aliments, qui en sont la principale source, sont transformés en monoglutamates dans les cellules intestinales. L'acide folique est présent dans de nombreux aliments, en particulier le foie et les légumes verts, mais il résiste mal à la chaleur. Les besoins en folate sont plus difficiles à établir que ceux en fer, car la disponibilité relative de l'acide ptéroylmonoglutamique et des polyglutamates n'est pas connue avec précision; ils sont plus élevés pendant la grossesse et, dans de nombreux cas, l'administration de folate est nécessaire au cours du troisième trimestre. Les besoins demeurent élevés chez les femmes allaitantes. Le tableau 3 (p. 666) indique l'apport en folate recommandé par l'OMS pour les divers groupes d'âge et pour les femmes enceintes ou allaitantes.

Le déficit en nutriments hémopoïétiques est surtout fréquent chez les femmes enceintes, mais on trouve en Asie des populations mâles où l'anémie peut atteindre une prévalence de 40% et plus. Même s'il s'agit d'anémie légère, cet état réduit la capacité de travail par le jeu de mécanismes encore mal connus. Les enquêtes de prévalence devraient porter avant tout sur les femmes enceintes, plus particulièrement durant le troisième trimestre de la grossesse. En cas de forte prévalence d'anémie ferriprive et lorsqu'il faut agir vite (grossesse), la supplémentation thérapeutique en fer s'impose, généralement par l'administration de tablettes d'un sel de fer comme le sulfate de fer (II). La dose à administrer sera évaluée en fonction du total des besoins: suppression du déficit, reconstitution du « stock » et besoins spéciaux de la croissance et de la grossesse. Il est urgent de mettre au point une préparation peu coûteuse à forte biodisponibilité et présentant peu d'effets secondaires. En ce qui concerne la supplémentation en folate, la dose n'a pas à être calculée de manière aussi précise et il suffira de s'assurer de la stabilité du folate contenu dans les tablettes.

Au contraire de la supplémentation, la fortification permet d'augmenter l'apport en nutriments sans infrastructure spéciale ni participation volontaire de la collectivité, mais c'est essentiellement une approche à long terme qui doit être assortie d'un programme de supplémentation dans les cas de carence grave. Pour la fortification en fer, on peut citer parmi les aliments « véhicules » — constituant la base de l'alimentation de la majorité de la population et dont la préparation ou le conditionnement sont suffisamment centralisés — la farine de froment en Europe septentrionale ou aux Etats-Unis d'Amérique, le sucre au Guatemala et le sel en Asie du Sud-Est. Les aliments pour bébés sont également un véhicule de choix. La préparation de fer utilisée doit avoir une bonne biodisponibilité et être stable à la cuisson et aux températures extrêmes. Divers essais sont en cours au Guatemala, en Inde et en Thaïlande. Les résultats de la fortification dépendent naturellement aussi de la nature des autres aliments consommés et il convient d'évaluer au préalable l'absorption de la préparation utilisée par rapport à celle de la « dose de référence ».

En conclusion, il semble, là comme ailleurs, que la combinaison d'un ensemble de mesures — parmi lesquelles il ne faut pas négliger l'éducation du public et du personnel de santé — est le meilleur moyen de lutte contre l'anémie nutritionnelle.